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Surveillance Recommendations for Children with Overgrowth Syndromes and Predisposition to Wilms Tumors and Hepatoblastoma

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Abstract

A number of genetic syndromes have been linked to increased risk for Wilms tumor (WT), hepatoblastoma (HB), and other embryonal tumors. Here, we outline these rare syndromes with at least a 1% risk to develop these tumors and recommend uniform tumor screening recommendations for North America. Specifically, for syndromes with increased risk for WT, we recommend renal ultrasounds every 3 months from birth (or the time of diagnosis) through the seventh birthday. For HB, we recommend screening with full abdominal ultrasound and alpha-fetoprotein serum measurements every 3 months from birth (or the time of diagnosis) through the fourth birthday. We recommend that when possible, these patients be evaluated and monitored by cancer predisposition specialists. At this time, these recommendations are not based on the differential risk between different genetic or epigenetic causes for each syndrome, which some European centers have implemented. This differentiated approach largely represents distinct practice environments between the United States and Europe, and these guidelines are designed to be a broad framework within which physicians and families can work together to implement specific screening. Further study is expected to lead to modifications of these recommendations. *Clin Cancer Res; 23(13); e115–e22. ©2017 AACR.*

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Introduction

Overgrowth syndromes represent a heterogeneous group of disorders that result in differing presentations based on the developmental pathways and organ systems affected. Renal tumors, typically Wilms tumors (WT), are reported in a number of these disorders with variable frequencies ranging from 1% to 90%. Clinically identified malformations and syndromes account for almost 18% of WT (1). In addition, several syndromes have an increased risk for hepatoblastoma (HB). Previously, screening guidelines have been largely based on those developed for Beckwith–Wiedemann syndrome (BWS) and *WT1*-related disorders. As part of the 2016 AACR Childhood Cancer Predisposition Workshop, an international committee of geneticists, oncologists, radiologists, and genetic counselors reviewed and made recommendations for the management of children with the syndrome-associated WT and other tumors present in these syndromes, and offered recommendations for tumor screening based on current published data and clinical practice. These recommendations were designed to be uniform for each tumor type being screened and to offer screening in cases with a 1% or greater risk when early detection is minimally invasive and significantly improves outcome.

Genetic Summary

Beckwith–Wiedemann syndrome (BWS) is a rare overgrowth syndrome classically characterized by pre- and postnatal constitutional and organ overgrowth, macroglossia, omphalocele/umbilical hernia, facial nevus flammeus, hemihyperplasia, and embryonal tumors (2). WT and HB are the most common tumor types reported; however, additional tumors have been reported, including neuroblastoma, rhabdomyosarcoma, pheochromocytoma, and adrenocortical carcinoma (3). Most cases of BWS are mosaic, and clinical features typically vary between patients with rare familial forms identified. Many cases of isolated

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hemihyperplasia (IHH) are considered a more subtle presentation of BWS leading to a spectrum of features due to a variety of structural, genetic, or epigenetic abnormalities localized to chromosome 11, termed the "11p Overgrowth Spectrum." IHH can have other non-11p causes as well. Several different clinical scoring systems have been presented to clarify the clinical diagnosis of BWS (2, 4). The incidence of BWS is one in 10,500 births (2), but with inclusion of the subtle cases with IHH, the incidence is likely higher. BWS is caused by the dysregulation of growth genes encoding both proteins and regulatory RNAs (*H19*, *IGF2*, and *CDKN1C*) on chromosome 11p15 that are imprinted and, therefore, normally expressed in a parent-of-origin–specific manner. At least 85% of BWS cases are not inherited, and most are due to epigenetic changes on chromosome 11p15, most commonly gain of methylation at one imprinting control region, IC1 (*H19*/*IGF2*:IG-DMR), or loss of methylation at a second imprinting control region, IC2 (*KCNQ1OT1:*TSS-DMR). Paternal uniparental isodisomy (pUPD11) for part or all of chromosome 11 (where both copies of this region of chromosome 11 are derived from the father) can also cause BWS. More rarely, mutations on the maternally derived copy of *CDKN1C*, paternally inherited duplications of the 11p15 region, or chromosomal rearrangements cause hereditary BWS. Given the complexity of the genetics, we recommend that any determination of recurrence risk for the parents or adults with BWS or testing of relatives be performed by a genetics health care professional.

Recent data from a large cohort of European patients with BWS suggest there is a correlation between tumor risk and the genetic or epigenetic cause of BWS, and it has been recommended that tumor screening should be based on the genetic or epigenetic cause (3, 5). Overall incidence of tumor risk is 5% to 10%, which represents an averaged statistic, as risk in patients with gain of methylation at IC1 was found to be 28%, whereas loss of methylation at IC2 was 2.6%, pUPD11 was 16%, and *CDKN1C* mutations was 6.7% (3). Frequency of tumor type varies by genotype as well (3, 5). WT and HB screening are recommended with abdominal/renal ultrasound and alpha-fetoprotein (AFP) measurements. The frequency and type of screening based on specific genetic or epigenetic changes are debated due to the differences in the acceptable risk and health care cultures in which the guidelines are implemented (6–8). These factors and current data were discussed at length by the international AACR workshop committee, and we acknowledge that consequences of the present knowledge may lead to differences in guidelines in countries with different health cultures. In the context of the United States, the committee recommends uniform screening based on tumor type for which patients are at risk, with the understanding that there is a need for continued discussion and that future screening may be tailored based on genetic cause and specific syndromes. Neuroblastoma screening is recommended for patients with *CDKN1C* mutations with urine catecholamines and chest radiographs, and those screening recommendations are outlined in the article by Kamihara and colleagues in this *CCR* Pediatric Oncology series (9). The incidence of tumor types in BWS other than those noted above (i.e., WT and HB) is not high enough to warrant specific screening recommendations at this time.

Bohring–Opitz syndrome (BOS) is a rare genetic syndrome characterized by severe growth and feeding problems, severe developmental delay/intellectual disability, typical facial appearance (trigonocephaly, retrognathia, prominent eyes with underdeveloped supraorbital ridges, upslanting palpebral fissures, depressed nasal bridge, anteverted nares, low-set and posteriorly rotated ears, glabellar nevus flammeus, low anterior hairline), microcephaly, forehead hirsutism, cleft lip and palate, retinal abnormalities, flexion anomalies of upper limbs with radial head dislocation and ulnar deviation of fingers ("BOS posture"), lower limb anomalies, structural brain anomalies, and seizures (10–15). About 40% of patients die in early childhood, typically from unexplained bradycardia, obstructive apnea, or pulmonary infections. Hoischen noted that in those who survive past infancy, distinctive facial features may fade over time (13). Females outnumber males approximately 3:1, with no evidence for difference in viability (13).

Multiple studies have demonstrated the transforming capacity of *ASXL1* mutations, suggesting *ASXL1* is a tumor-suppressor gene (13, 15–19). Thus, there is an increased tumor risk in patients with BOS. Two patients presented with bilateral WT with confirmed *ASXL1* mutations: one diagnosed at age 2 years and the other at age 6 years. In the 43 cases reported by Russell and colleagues (2015), two patients developed WT and one had nephroblastomatosis leading to a renal neoplasm incidence of 7% (15). The small number of reported patients with BOS and high infant mortality rate indicates that the true cancer risk may be higher than reported. WT screening guidelines as used for BWS have previously been recommended and the AACR workshop committee concurred with that recommendation (15).

Mulibrey (muscle, liver, brain, and eye) nanism is a rare, autosomal recessive growth disorder with prenatal onset that includes severe growth retardation, distinct dysmorphic features, constrictive pericarditis, hepatomegaly, male infertility, insulin resistance, and metabolic deficiencies (20, 21). Approximately 130 cases are known worldwide, with 89 originating from Finland (20). Mulibrey nanism is caused by biallelic mutations in *TRIM37* on chromosome 17q22.

Mulibrey nanism is associated with development of a wide array of benign and malignant tumors. A systematic review revealed a total of 210 tumors in 66 of the 89 (74%) reported Finnish patients (21). Benign tumors included cysts within various organs, peliosis of the liver, adrenal adenoma, parathyroid adenoma, thyroid nodules, pancreatic cystadenoma, renal angiomyolipoma, ovarian fibrothecoma, pheochromocytoma, and central nervous system (CNS) Langerhans cell histiocytosis (20). Thirteen (15%) of these patients developed malignant tumors, including WT ($n = 5$; median age, 2.5 years; range, 2.2–3.7 years), renal papillary carcinoma ($n = 3$; median age, 22.3 years; range, 17–28 years), papillary thyroid carcinoma ($n = 3$; median age, 32.1; range, 28–40 years), and single cases of medullary thyroid carcinoma, ovarian carcinoma, endometrial carcinoma, and acute lymphoblastic leukemia (20). On the basis of these results, screening for WT using renal ultrasound was recommended by the AACR workshop committee for children with Mulibrey nanism. Screening for renal, thyroid, ovarian, and endometrial carcinomas could also be considered for affected adults.

Perlman syndrome is a rare congenital overgrowth syndrome inherited as an autosomal recessive trait (22–24). Characteristic features include polyhydramnios, macrosomia, characteristic facial dysmorphology (broad depressed nasal bridge, everted V-shape upper lip, low-set ears, deep-set eyes, and prominent forehead), renal dysplasia and nephroblastomatosis, and multiple congenital anomalies. Fifty-three percent of children with Perlman syndrome die in the neonatal period from a variety of

causes including renal failure, hypoxia, and pulmonary hypoplasia (22–24). The kidneys show nephroblastomatosis in about 75% of cases (25). In those that survive the neonatal period, developmental delay is common and most patients appear to develop WT. On average, WT occurs at an early age (<2 years compared with 3 to 4 years in sporadic WT), and bilateral WT are common (55%; refs. 22, 24, 26).

Perlman syndrome may be differentiated from other congenital overgrowth disorders such as BWS and Simpson–Golabi–Behmel syndrome (SGBS) by the presence of features including fetal ascites and characteristic facial dysmorphism in the absence of macroglossia, anterior abdominal wall defects, polydactyly, and other features. In addition, a molecular diagnosis of Perlman syndrome can be made by the presence of inactivating mutations in *DIS3L2* on chromosome 2q37.1, whose product has been implicated in miRNA degradation (27, 28). In view of the high risk of WT, it has been suggested that children affected with Perlman syndrome should be offered regular surveillance similar to that for children with BWS (29).

SGBS is characterized by pre- and postnatal macrosomia, distinctive craniofacies (including macrocephaly, coarse facial features, macrostomia, macroglossia, palatal abnormalities), and commonly, mild-to-severe intellectual disability with or without structural brain anomalies. Other variable findings include supernumerary nipples, diastasis recti/umbilical hernia, congenital heart defects, diaphragmatic hernia, genitourinary defects, and gastrointestinal (GI) anomalies. Skeletal anomalies can include vertebral fusion, scoliosis, rib anomalies, and congenital hip dislocation. Hand anomalies can include large hands and postaxial polydactyly. Physical features distinguishing SGBS from BWS are ocular hypertelorism, a large mouth, coarse facial features, supernumerary nipples, and persistent overgrowth throughout life.

SGBS is X-linked and caused by mutation or deletion of the glypican genes *GPC3* (30) or *GPC4* (31). Although SGBS is X-linked and generally restricted to males, the SGBS phenotype has been observed in females (32, 33).

Tumor types seen in SGBS include multiple reports of WT and nephroblastomatosis (34), five reports of liver tumors in children (34–38), and neuroblastoma (39). One case of medulloblastoma in SGBS has been reported (40). Currently, there do not appear to be specific genotype–phenotype correlations, and deletions and truncation mutations have been reported with and without tumor development. Tumor screening similar to BWS screening has previously been used in these patients (41). Some have also suggested utilizing the β-HCG tumor marker due to previous reports of germ cell tumors in SGBS; however, this is not a widespread recommendation (35, 40). No screening recommendations have been made for CNS tumors in SGBS.

Trisomy 18 (Edwards syndrome) is the second most common constitutional chromosomal abnormality after trisomy 21, occurring in 1:6,000 to 1:8,000 live births (42). Mosaic and partial trisomy 18 also occur. Trisomy 18 is characterized by a variety of major and minor malformations, growth retardation, psychomotor delays, and intellectual disability (42, 43). Only 5% to 10% of affected infants live past the first year, and the infants who survive this period are at increased risk to develop benign and malignant tumors (44). The high mortality rate is a result of many factors including cardiac and renal malformations, feeding difficulties, sepsis, and central apnea (45). Children with mosaic or partial trisomy 18 have a higher life expectancy than the children with full trisomy 18.

A systematic review found 45 malignancies in 56 patients, mostly HB and WT (44). Nephroblastomatosis was also reported in autopsies of infants with trisomy 18 who did not die from a WT (46, 47). The risk for WT development is estimated to be approximately 1% (48). Benign tumors, including cardiac and skin tumors, have additionally been reported (44). The rate of cancer in this population may be underestimated given the high infant mortality rate observed. Cancer screening for trisomy 18 is controversial given the poor prognosis and tendency to avoid surgery and other invasive procedures. The AACR workshop committee recommendations are outlined below.

WT1-related syndromes include WAGR (WT, aniridia, genitourinary abnormalities, retardation) syndrome, Denys–Drash Syndrome (DDS), and Frasier Syndrome (FS). *WT1* encodes for a zinc finger–containing protein with multiple isoforms (49, 50). This protein acts as a transcription factor during development, regulating cell growth and differentiation in the kidneys, gonads, spleen, and mesothelium (49, 50). DDS and FS may represent variations along a phenotypic spectrum (51). In all *WT1*-related syndromes, inheritance is autosomal dominant, the penetrance is mutation dependent, the expressivity is variable, and most mutations are *de novo*.

WAGR syndrome is characterized by WT, aniridia, genitourinary abnormalities, and intellectual disability (41). A significant risk of nephropathy also exists (52). This constellation of features is due to contiguous gene deletions in chromosome 11p13 including *WT1*, *PAX6*, and other genes. DDS is characterized by WT, nephrotic syndrome (due to mesangial sclerosis), and ambiguous genitalia/gonadal dysgenesis (in affected individuals with 46,XY karyotype). The syndrome is predominantly caused by missense mutations in exon 8 or 9 of *WT1* (53, 54). FS is characterized by focal segmental glomerulosclerosis and ambiguous genitalia/gonadal dysgenesis and risk of gonadoblastoma (in affected individuals with 46,XY karyotype and dysgenetic gonads). Mutations in the *WT1* intron 9 donor splice site are associated with this condition.

Overall, *WT1* germline mutations (either somatic only or inherited) are found in up to 11% of occurrences of WT (1, 55, 56). The median age of WT diagnosis is around 1 year of age in *WT1*-affected individuals, about 2 to 3 years earlier than the age of WT diagnosis in children without a germline *WT1* mutation. There have been reports of children with *WT1* mutations developing WT up to 8 years of age (54). The risk of WT development varies among the *WT1*-related syndromes. The risk of WT in WAGR is approximately 50% (54). In DDS, it is greater than 90% (54). In FS, multiple cases of WT have been reported (54). Several other genotype–phenotype correlations relevant to WT risk have also been reported. The greatest risk for WT may be related to truncating mutations in the exon 8/9 hotspot (57, 58). Furthermore, the risk of bilateral WT is significantly greater with truncating mutations than with missense mutations (57, 58).

WT1-related gonadoblastoma occurs in the context of disordered sexual development in FS or DDS individuals with 46,XY karotype. In these patients, the gonadoblastoma appears to be directly related to the presence of gonadal dysgenesis and is equally likely to occur in both FS and DDS, with an estimated risk level greater than 40% (58, 59). Although most gonadoblastomas develop in adolescents or young adults, occurrences in children as young as infants have been described (59–61). The risk of gonadoblastoma is low when the sex matches the karyotype (58). However, an evaluation for gonadal dysgenesis is indicated

in patients with karyotype 46,XY, and if present, gonadectomy is generally recommended. Management of gonadoblastoma risk in individuals with suspected gonadal dysgenesis per recent evidence-based guidelines detailed elsewhere is recommended (62). These guidelines encompass the initial evaluation for gonadal dysgenesis (including hormonal assessment and imaging) and considerations for the timing of gonadectomy. The AACR workshop committee recommendations are discussed below.

Additional causes of WT include the presence of somatic chromosome copy-number changes affecting chromosome 2q37 and for the *MYCN* gene at 2p24.3 (63–65). Germline changes at these loci have also been reported in patients presenting with WT, and, therefore, WT risk should also be considered in patients with germline *MYCN* copy-number gains (2p24.3) or 2q37 microdeletions (66, 67). The incidence of patients with these genetic changes is rare, and the actual incidence of WT in these populations needs further study. *DICER1* mutations have also been linked to WT, and further discussion of *DICER1* can be found in the article by Schultz and colleagues (68) in this series. Mosaic variegated aneuploidy is another rare recessive set of disorders in which WT has been reported in multiple patients (54).

There are several other overgrowth syndromes, including *PIK3CA*-related overgrowth spectrum, Sotos syndrome, and Weaver syndrome, for which incidental cases of cancer have been reported. However, with cancer risk estimates below 1%, cancer screening is not recommended. Weaver and Sotos syndromes are discussed in the article by Villani and colleagues (69) in this series.

Cancer Screening/Surveillance Protocols

The AACR workshop recommendations reflect the health care culture in North America and may differ from that of other parts of the world. For instance, WT screening is recommended in North America based on an acceptable risk model of 1% for all syndromes as listed in Table 1. However, in Europe, a threshold of 2% is typically used. These recommendations are based on the advantage of having a consistent, inclusive, universal protocol that can be effectively applied to all patients for a specific tumor type, where screening is minimally invasive and the outcome of early detection for a specific tumor type offers significant improvement in morbidity and mortality. We acknowledge that uniform recommendations may result in some patients being screened more frequently and for a longer duration than some clinicians have previously determined to be necessary. Therefore, these recommendations should be discussed with each family, and the family needs to be counseled in the context of their specific syndrome and the tumor risk in their case by physicians and/or genetic counselors' knowledgeable on this topic [see article by Druker and colleagues in this series (70)]. Surveillance can be further tailored on the basis of the disorder and knowledge regarding the specific characteristics of the tumors that occur in the syndrome, especially as the burden that accompanies any surveillance scheme is perceived differently in some European countries.

Developing guidelines for tumor screening is challenging and needs to take into account current data available for tumor risk and the medical and societal context in which the screening is being implemented. Although there is emerging evidence of different cancer risks based on genetic or epigenetic subgroups for certain syndromes, and several European countries now use subgroup-specific recommendations for WT screening particularly in BWS, these practices have not yet been adopted in the United States. Thus, recommendations are likely to continue to evolve over time. Furthermore, age ranges of tumor risk may vary between syndromic versus sporadic causes of WT. However, to simplify these screening recommendations, our AACR workshop committee proposes a uniform screening approach for all syndromes with a risk of WT greater than 1%. Additional screening for HB by serum AFP measurement is recommended in BWS, trisomy 18, and SGBS.

These recommendations are based on screening that will lead to earlier stage tumor detection (71, 72) and have been designed to cover the age range in which 90% to 95% of tumors will present (41). The interval of WT screening is based on the increased risk of interval tumor development when screening is spaced beyond 4 months (73). As the rate of tumor growth is expected to be the same regardless of age, the recommended frequency of screening does not change as the patient ages. As further data are collected and with improved access to and understanding of genetic testing by both families and physicians, screening recommendations in the future will likely evolve to incorporate distinctions based on genetic causes of each syndrome and between different syndromic causes of WT and HB.

The goal of the AACR workshop was to present screening recommendations based on tumor type when the risk for a tumor within a syndrome was above a specified threshold. These guidelines were meant to be uniform across a tumor type, not tailored to a specific syndrome or genetic etiology. However, it is important to note that the field of cancer genetics is learning that risk of a specific tumor type varies by underlying syndrome, and even by genetic cause within the same syndrome; therefore, additional guidelines will be needed in the future to diversify screening based on syndrome and genetic cause.

Table 1. WT risk associated with different overgrowth syndromes

Syndrome	Recommended screening	Risk of WT	Median age of WT occurrence	References
BWS	WT, HB	4.1%	24 months	(3, 5)
Hemihypertrophy	WT, HB	3%–4%	37 months	(83)
Bohring–Optiz	WT	6.9%	24 months	(15)
Mulibrey nanism	WT	6.7%	30 months	(20)
Perlman	WT	75%	<24 months	(96, 97)
Simpson–Golabi–Behmel	WT, HB	8%	Undefined	(34, 98)
Trisomy 18	WT, HB	>1%	68 months	(44, 99)
WAGR	WT	50%	Most 5–9 y 22 months	(52–54, 100)
Denys–Drash	WT	>90%	Most <8 y 12 months	(101)
Frasier	WT	Several cases	Most <3 y Undefined	(102)

Abbreviation: y, years.

WT screening

The mean age from a large meta-analysis for WT diagnosis in BWS is 24 months (3), and most will occur prior to age 4 years. However, limited published data exist regarding the development of WT in the 4- to 7-year age range. A combined study of 324 patients with WT and either BWS or IHH showed that 69% of WT occurred prior to age 4 years, 81% before age 5 years, 87% before age 6 years, and 93% prior to age 8 years (74). This cohort represents a mixture of BWS and IHH patients with WT, and molecular data were not provided. Therefore, it may be that causes other than the 11p Overgrowth Spectrum were present in these cohort participants and could be responsible for WT occurrence after 4 years of age. Regardless, these data demonstrate that a range of age distribution exists in patients with WT and a phenotype of BWS and IHH, including a small but measurable percentage up to the age of 8 years. These data are not included in the recent meta-analyses due to the absence of molecular data (3, 5). It remains challenging to determine the age to stop screening, because the age of tumor formation does not follow a normal distribution based on the median age of onset. As seen with neuroblastoma, although the median age may be 2 years, 98% of tumors occur before age 10 years, and, therefore, screening is recommended until 10 years, as discussed in the article by Kamihara and colleagues in this series (9). Taken together, these data suggest that screening for WT should continue through age 6 to 7 years, with more data needed to be collected to determine the exact age at which to end screening.

For WT, starting at birth (or the time of diagnosis of the specific syndrome), we recommend renal ultrasound screening including the adrenal glands every 3 months through the child's seventh birthday. For syndromes in which HB is also a risk (BWS/IHH, trisomy 18, SGBS), full abdominal ultrasound instead of renal-only ultrasound is recommended every 3 months through the child's fourth birthday. After the fourth birthday, these patients can be monitored with renal ultrasound every 3 months until the seventh birthday. Physical examination by a specialist (geneticist or pediatric oncologist) twice yearly is recommended and should include ongoing education regarding tumor manifestations, reinforcing the rationale for screening and compliance with the screening regimen, and other syndrome-specific manifestations.

HB screening

HB screening is recommended in BWS due to the increased relative risk of 2,280 times that of the healthy population (75). For HB in BWS, most HB occur within the first year, with the oldest reported at 30 months (3); this suggests that HB screening could start at birth and continue up to the fourth birthday. AFP screening is sensitive for HB (76, 77) and can be used to distinguish hemangiomas compared with HB detected by imaging (78, 79). AFP elevation often precedes detection by ultrasound (76, 80), as HB can grow rapidly and screening results in detection at a lower stage (77, 81–83). Families appear to be comforted by early diagnosis and regular medical checks (6), and HB detected at earlier stages have better prognosis. Previous AFP interval screening recommendations have varied between 6 weeks and 3 months. In the general pediatric population, it has been recommended that elevated AFPs be remeasured at 2- to 4-week intervals to evaluate for pathologic causes of elevated AFP (84). In the BWS population, AFP levels may be elevated above that in other populations, but if a modest elevation is observed, repeat measurements every 6 weeks have been recommended (85). These recommendations are presented in the literature (2, 86), but no systematic studies have demonstrated improved outcomes of 6 weeks versus 3 months in detecting HB. In some cases, more frequent screening may be warranted (80).

For HB screening, we recommend full abdominal ultrasound and simultaneous serum AFP screening every 3 months starting at birth (or at the time of diagnosis) and continuing through the child's fourth birthday for patients with BWS/IHH, trisomy 18, and SGBS. The question of screening in the presence of familial adenomatous polyposis is covered in the article by Achatz and colleagues in this series (87). In monitoring AFP levels, the individual value needs to be interpreted in the context of the AFP trend over time, with an expectation of declining values through infancy. Importantly, AFP results need to be interpreted on the basis of normal BWS values, which tend to be elevated over the first years of life compared with normal pediatric values (88–90). AFP values also should be interpreted in the context of the clinical picture, the age of the patient, and the most recent imaging. In addition, interpretation should be done by, or in consultation with, physicians familiar with AFP monitoring in these syndromes, particularly geneticists and oncologists in cancer predisposition programs. Small rises within the reference ranges should not trigger additional testing, as these can be due to intercurrent illness or other factors such as teething, which emphasizes the importance of a good medical history taken at the time AFP values are collected.

Large rises in AFP values (greater than 50–100 ng/mL) should be further investigated, first with a repeat AFP in 6 weeks and a re-examination of the most recent ultrasound imaging. Several different intervals for repeat testing have been recommended in a few reported cases, but it is unclear that repeating the AFP measurement sooner than 6 weeks alters the clinical outcome (80, 91). If two successive increases occur, further imaging by MRI is recommended. In cases of significantly larger increases (greater than 1,000 ng/mL), repeat testing to validate the value is recommended, and if validated, one should proceed directly to additional imaging.

Radiologic considerations

Ultrasonography is the optimal screening tool used to detect a mass in the liver or kidneys. It is widely available, lacks ionizing radiation, and can be performed without sedation. Preparation for an abdominal or renal ultrasound does not require fasting. Ultrasonography has a high sensitivity for detecting hepatic masses (92). The main diagnostic consideration in this patient population besides HB is infantile hepatic hemangioma, a benign vascular neoplasm, seen with greater incidence in BWS/IHH than the general population. Classic ultrasound features of hemangioma include homogeneous echotexture, hyper or hypoechoic, and increased peripheral vascularity on Doppler interrogation. Hemangiomas can be solitary, multifocal, or diffuse. Any atypical features such as lobulated margins, chunky calcifications, heterogeneity indicating hemorrhage or necrosis, or diminished vascularity raise the concern for HB, and correlation with AFP should be performed (78, 79). In multifocal and diffuse cases, the possibility of metastatic neuroblastoma should be considered and an adrenal primary tumor should be excluded. Patients with rising AFPs should be evaluated by MRI with a hepatobiliary contrast agent or contrast-enhanced portal venous phase CT. MRI is preferred due to the lack of ionizing radiation and superior lesion characterization using multiphase contrast

enhancement and diffusion-weighted imaging. Contrast-enhanced ultrasound using gas-filled microbubbles is an emerging tool used to evaluate liver lesions (93). An IV is required for administration of the contrast agent, but sedation is not required.

Surgical considerations

In syndromic WT, given the increased recurrence risk in the ipsilateral or contralateral kidney, nephron-sparing surgery is recommended if possible (94). MRI is considered the ideal imaging modality used for detection of multiple tumors and nephrogenic rests and for preoperative evaluation in consideration of partial nephrectomy. Infiltration of adjacent structures, central location, tumor thrombus, tumor rupture, or collecting system involvement are features that help the surgeon consider whether a partial or complete nephrectomy is the correct choice for the patient (95).

General considerations

Historically, most children with the disorders included in this article were monitored by their general pediatricians and only referred to oncology if a malignancy developed. Although access to academic centers with multidisciplinary subspecialty clinics may not always be practical or readily available, physicians are encouraged to refer patients to such clinics if at all possible. This heterogeneous group of rare disorders can display many subtle features with variable penetrance and is accompanied by a rapidly expanding knowledge based on the genetic, epigenetic, and therapeutic implications attendant with each, making it very difficult for the general pediatrician to stay abreast of the latest information. Once referred, screening can be performed locally, and the specialists can work with the general pediatricians to manage any abnormal results and the patients' ongoing screening.

Thus, critical imperatives in the surveillance of these conditions are: (i) having longitudinal radiologic assessments performed by the same group and evaluated by the same individuals (ideally pediatric radiologists), and if warranted, (ii) having AFP values performed in the same laboratory each time, as much as reasonably possible. Overall, outcomes for these patients will be optimized by the longitudinal integration of clinical and research data by groups providing uniform surveillance and intervention based on the guidelines recommended herein.

In addition, in cases where a tumor develops, syndromic patients should be considered in the context of both immediate post-tumor screening and should return to pre-tumor screening schedules once the initial post-tumor screening recommendations are completed. On the basis of current data, most of these syndromes are not associated with an increased risk of adult-onset cancers. Thus, as the child ages past the need for WT and HB screening, there should be a discussion with the parents whether further cancer screening is indicated.

Finally, as genetic and epigenetic understanding of the mechanism underlying tumor formation in these patients continues to evolve, these screening recommendations are likely to be further stratified. For those changes to occur, further discussion regarding the role of "health care cultures," which includes determination of acceptable risk, medical systems, and cultural context of medical practice, needs to occur. This article is designed to provide the most appropriate and broadest recommendations for this varied group of patients susceptible to WT and HB. However, implementation of these recommendations still falls to the individual physicians within the medical environment and community in which they practice. In addition, a critical part of the implementation of these recommendations is the practitioner's discussion with the patient and the patient's family regarding tumor screening.

Conclusions

In summary, we recommend specific WT and HB screening guidelines for patients in the United States with genetic syndromes that lead to a risk of $\geq$1% for these tumors. This screening is recommended uniformly for all of these syndromes and should be monitored by cancer predisposition experts whenever possible and implemented in discussion with each patient and his or her family. The next step to improve a patient-personalized screening strategy for WT and HB will need to include collection of additional genetic and clinical outcome data to determine if screening should be personalized based on genetic or epigenetic change for many of the syndromes discussed above. As we implement these screening programs in our pediatric communities, we will need to continually reevaluate the effectiveness of these screening guidelines and adjust them as new information is collected.

Disclosure of Potential Conflicts of Interest

S.E. Plon is a consultant/advisory board member for Baylor Genetics. No potential conflicts of interest were disclosed by the other authors.

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